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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,771	03/22/2004	Vivian Y.H. Hook	066817-0024	2420

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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
03/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SIP_Docket@mwe.com

Office Action Summary	Application No.	Applicant(s)	
	10/806,771	HOOK, VIVIAN Y.H.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-20* is/are pending in the application.

4a) Of the above claim(s) *2 and 5-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 4, and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/25/2010 has been entered.

The Applicants Amendments to the claims received on 1/25/2010 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 1/25/2010 are hereby withdrawn.

Claim(s) 2-20 are pending. No claims have been amended. Claims 2, 5-19 are withdrawn. Claims 3, 4, and 20 are hereby examined on the merits.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The instantly claimed invention is not drawn to a treatment for Alzheimer's, and should be changed to reflect the elected invention of an assay.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 3, 4, and the new Claim 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagao et al, "Synthesis of a new class of cathepsin B inhibitors exploiting a unique reaction cascade," Tetrahedron Letters, 41 (2000), 2419-2424 and Mackay EA et al "A possible role for cathepsins D, E, and B in the processing of beta-amyloid precursor protein in Alzheimer's disease," Eur J Biochem. 1997 Mar 1;244(2):414-25.

The instant claims are drawn to a method of selecting an agent that prevents the cleavage of an APP by the proteolytic action of cathepsin B.

Nagao et al teaches an assay where cathepsin B inhibitors are incubated in the presence of a cathepsin B peptide substrate, Z-L-Phe-L-Arg-MCA, see page 2421 and last paragraph for the assay. Nagao et al does not teach the use of APP as a cathepsin B substrate.

Mackay et al discloses the proteolytic action of cathepsin D, E, and B (Applicant's elected species), on the amyloid precursor protein (APP). Mackay et al teaches the use of MALDI-TOF mass spectroscopy to identify the position of cleavage of cathepsin D, E, and B, see Figure 3 and Figure 5. Mackay et al does not teach the use of an inhibitor of cathepsin D, E, or B in the assay to inhibit the action of cathepsin B.

The difference between what is taught by the prior art and that instantly claimed is that the instant invention claims an assay to screen for inhibitors of cathepsin B toward APP, and the prior art teaches that there are cathepsin B inhibitor assays already developed but do not use APP as the substrate (Nagao et al) but that APP is a substrate of cathepsin B (Mackay et al).

It would have been obvious to one of ordinary skill in the art to modify the assay taught by Nagao et al to substitute the B peptide substrate, Z-L-Phe-L-Arg-MCA, with that of APP. One would have been motivated to do this because Mackay teaches that APP is a substrate for cathepsin B. One would have had a reasonable expectation of success in substituting APP for Z-L-Phe-L-Arg-MCA because cathepsin B can hydrolyze both Z-L-Phe-L-Arg-MCA and APP, and those inhibitors blocked cathepsin B and would also block the hydrolysis of APP. One would be further motivated to continue screening for compounds that inhibit the catalysis of APP because the hydrolytic fragments are known to be involved in the formation of Alzheimer's disease, and that one would be motivated to identify theses inhibitors for potential therapeutic use. Conversely, from the combined teaching of the Mackay et al and Nagao et al references, it would have been obvious to modify the Mackay et al teachings to add the inhibitors of Nagao et al, as well as any other compound, to determine whether the compound blocked cathepsin B activity and produced full length APP proteins as determined by MALDI-TOF mass spectroscopy. One would have a reasonable expectation of success because of the detailed information revealed from MALDI-TOF mass spectroscopy, which include the position of cleavage by mass if the compound did not inhibit cathepsin B. From the teachings of the references supra, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, and the invention as claimed, is rejected under 35 U.S.C. 103(a).

Applicant's Arguments

Applicants arguments have been carefully considered but are not deemed persuasive to overcome the rejection. Applicants have *maintained* there is no motivation to combine the references. It is argued that there

...would have been no motivation to combine the two cited prior art references, which clearly show that the substrate used in the assays described by Nagao et al., which is a dipeptide capped at both ends, is distinct from the cleavage sites recognized by cathepsin B in the APP protein. Figure 6, panel C, shows the cleavage sites recognized by cathepsin B and not one of them consists of the amino acids F - Phenylalanine (Phe/F) and R - Arginine (Arg/R) that make up the dipeptide of Nagao et al. There is no indication in Nagao et al. that the assay would work if the short dipeptide were to be replaced with a considerably longer substrate that does not even contain the Phe-Arg cleavage site known in the art to be recognized by cathepsin B.

It is further argued that the since APP lacks Phe-Arg recognition site, it would not be a substrate for cathepsin B, see page 6 of the response. Lastly, it is argued that the "*Mackay et al. reference shows that the beta-secretase activity of cathepsin B implicates substrate cleavage sites different and distinct from those of the dipeptide substrate used by Nagao et al.*"

Response to Arguments

Applicant's arguments are not persuasive because the Mackay reference teaches that APP is a substrate for Cathepsin B. Just because the cleavage site is different between the two substrates, does not teach away from substituting APP for Z-L-Phe-L-Arg-MCA as both are substrates for the Cathepsin B. Applicant's statement that "*the Mackay et al. reference shows that the beta-secretase activity of cathepsin B implicates substrate cleavage sites different and distinct from those of the dipeptide*

substrate used by Nagao et al," is a clear admission that the cathepsin B cleaves APP, regardless of the recognition site on the molecule. Therefore, one would have clear motivation to substitute one substrate for another in the assay. There is no teaching away because the Mackay et al reference shows that cathepsin B cleaves APP. Therefore, the rejection is maintained for the reasons of record.

Conclusion

No claims are allowed.

Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

/Thomas S Heard/

Examiner, Art Unit 1654

/Cecilia Tsang/

Supervisory Patent Examiner, Art Unit 1654